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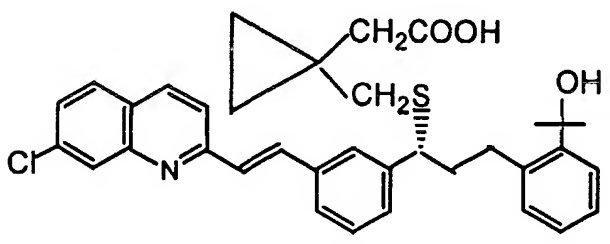


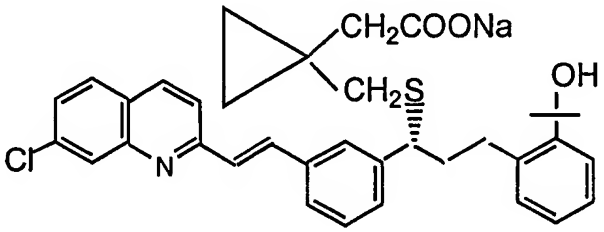
(I)

(57) Abstract: The present invention relates to novel anhydrous amorphous forms of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same. Montelukast is a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent. Montelukast is represented by the formula (I).

NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT

The present invention relates to novel anhydrous amorphous forms of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same.

Montelukast Sodium, chemically known as [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid (Montelukast) sodium salt is represented by the formula:



Montelukast sodium, a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and is hence useful in the treatment of angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection.

EP 480717 discloses certain substituted quinoline compounds including [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium), and methods for their preparation.

The reported synthesis of Montelukast Sodium proceeds through corresponding methyl ester and involves coupling methyl 1-(mercaptomethyl) cyclopropane-acetate with a mesylate generated *in situ*. The methyl ester of Montelukast free acid is hydrolyzed to the free acid and the latter converted directly to the corresponding sodium salt. This process is not particularly suitable for large-scale production because it requires tedious chromatographic purification of the methyl ester intermediate and/or the final product, and the product yields are low.

WO Patent Application 95/18107 discloses an improved process for the preparation of crystalline Montelukast sodium salt, which comprises the generation of dilithium dianion of 1-(mercaptomethyl) cyclopropaneacetic acid followed by condensation with 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-methanesulfonyloxypropyl) phenyl)-2-propanol to afford the Montelukast acid which is then converted, via dicyclohexyl amine salt, to its corresponding sodium salt. The obtained sodium salt is further crystallized from a mixture of toluene: acetonitrile to obtain crystalline Montelukast sodium.

The PCT application further designates the products obtained as per EP 480717 as amorphous sodium salts, which are hydrated and often not ideal for pharmaceutical formulation.

It has been disclosed earlier that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms [Konne T., Chem pharm Bull., 38, 2003(1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. An amorphous form of Cefuroxime axetil is a good example for exhibiting higher bioavailability than the crystalline form.

Since Montelukast sodium is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and amorphous forms of a number of drugs have been disclosed to exhibit different dissolution characteristics and in some cases different bioavailability patterns when compared to crystalline forms, the present invention, hence, aims to provide novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts and to processes for the preparation thereof.

The present invention also provides pharmaceutical compositions and pharmaceutical methods of treatment using novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

Another embodiment of the present invention is to provide methods for the preparation of the anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) which comprises dissolution of

Montelukast free acid in aromatic hydrocarbon solvent or halogenated solvent and converting the free acid to its alkali salt, accompanied by addition of a cyclic or acyclic hydrocarbon solvent or mixtures thereof, followed by isolation of the desired compound.

Still another embodiment of the present invention is to provide pharmaceutical formulations containing an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt.

An additional embodiment of the present invention is to provide pharmaceutical methods of treatment using anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

Brief Description Of The Accompanying Drawing

Fig. 1 is X-ray powder diffractogram of novel anhydrous amorphous form of Montelukast Sodium.

The present invention provides novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts, preferably, anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt.

The present invention also provides a process for preparation of anhydrous amorphous forms of Montelukast alkali metal salts. The anhydrous amorphous forms of Montelukast alkali metal salts are prepared by dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon. The solution of free acid of Montelukast is converted into alkali salt by use of alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C_1-C_4 straight or branched chain alcohol or by use of alcoholic alkaline metal hydroxide or an alcoholic metal alkoxide.

One process for preparing amorphous forms of Montelukast alkali metal salts comprises:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent; and

iv) isolating amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of amorphous forms of Montelukast alkali metal salts, which comprises:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent; and

iv) isolating amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

The alkaline metal may be selected from calcium, sodium, potassium, or magnesium. Preferably, the alkaline metal is sodium.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

i) dissolving the free acid of Montelukast sodium in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding sodium salt using sodium hydroxide or sodium alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

i) dissolving the free acid of Montelukast sodium in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

In a preferred embodiment of the invention, the ratio of Montelukast free acid to C_1-C_2 halogenated solvent or C_7-C_8 aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.

In a preferred embodiment of the invention, the ratio of Montelukast acid to C_1-C_4 straight or branched chain alcohol is 1:2-3 w/v.

In a preferred embodiment of the invention, the molar ratio of Montelukast acid to alkali metal hydroxide or alkaline metal alkoxide is 1:0.98 – 1.02, preferably, 1:1. In a preferred embodiment of the invention, the ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v wherein the ratio of Montelukast acid to alkaline metal in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:0.98 – 1.02 w/v. In step iii), the ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.

In precipitation of Montelukast alkali salt in step iv) the ratio of C_1-C_2 halogenated solvent or C_7-C_8 aromatic solvent to the C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon is 1:5 to 1:13 v/v. The preferred ratio is 1:6.5 v/v. This ratio is based on the amount of the C_1-C_2 halogenated solvent or C_7-C_8 solvent added in step iii).

The C_1-C_2 halogenated solvent may be selected from chloroform, dichloromethane or dichloroethane, preferably dichloromethane. The C_7-C_8 aromatic hydrocarbon solvent may be selected from toluene, ethyl benzene or xylene, preferably toluene.

The alkali used in step ii) may be selected from sodium hydroxide, sodium methoxide, sodium ethoxide, methanolic sodium hydroxide, ethanolic sodium hydroxide, methanolic sodium methoxide, ethanolic sodium methoxide, methanolic sodium ethoxide, ethanolic sodium ethoxide, calcium hydroxide, calcium methoxide, calcium ethoxide, methanolic calcium hydroxide, ethanolic calcium hydroxide, methanolic calcium methoxide, ethanolic calcium methoxide, methanolic calcium ethoxide, ethanolic calcium ethoxide, potassium hydroxide, potassium methoxide, potassium ethoxide, methanolic potassium hydroxide, ethanolic potassium hydroxide, methanolic potassium methoxide, ethanolic potassium methoxide, methanolic potassium ethoxide, ethanolic potassium ethoxide, magnesium hydroxide, magnesium methoxide, magnesium ethoxide, methanolic magnesium hydroxide, ethanolic magnesium hydroxide, methanolic magnesium methoxide, ethanolic magnesium methoxide, methanolic magnesium ethoxide, ethanolic magnesium ethoxide, preferably the alkali is sodium hydroxide.

The C_1-C_4 straight or branched chain alcohol may be selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary.butanol, preferably methanol. The C_5-C_7 acyclic solvent may be selected from pentane, hexane, n-hexane, n-heptane or n-octane, preferably hexane or n-heptane. The C_5-C_8 cyclic hydrocarbon solvent may be selected from cyclopentane, cyclohexane or cycloheptane, preferably cyclohexane.

Novel anhydrous amorphous forms of Montelukast alkali salts may be characterized by the X-Ray powder diffraction pattern. The present invention provides anhydrous amorphous form of Montelukast Sodium that is characterized by its X Ray powder diffraction, substantially in accordance with Figure 1. The X-Ray diffraction pattern of anhydrous amorphous form of Montelukast Sodium was measured on a Rigaku Dmax 2000 with Cu K alpha-1 ISOKV/34mA, Degrees scanned: 3-45 degrees. Scan speed 3 degree/min.

The compounds of this invention can be used to prevent the synthesis, the action or the release of SRS-A or leukotrienes.

The ability of the compounds of the present invention to antagonize the actions of the leukotrienes makes them useful for preventing or reversing the symptoms induced by the leukotrienes in a mammal including a human subject. This antagonism of the actions of leukotrienes indicates that the compounds of this invention and pharmaceutical compositions thereof are useful to treat, prevent, or ameliorate in mammals and especially in humans: 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies and allergic reactions such as allergic rhinitis, contact, allergic conjunctivitis, and the like, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, atopic eczema, and the like, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, platelet aggregation and the like, 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions including inflammatory diseases such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, endotoxemia and the like, 12) allograft rejection, 13) prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor, 14) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 15) cholecystitis and 16) glomerular nephritis.

The compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea' ischemia, noxious agent-induced damage of necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatodxix agents such as CCl_4 and D-galactosamine; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure. The compounds also exhibit cytoprotective action. (See EP 0480717).

The magnitude of prophylactic or therapeutic dose of a compound of this invention will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of this invention and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range for anti-asthmatic, anti-allergic or anti-inflammatory use and generally, uses other

than cytoprotection, lie within the range of from 0.001 mg to 100 mg per kg body weight of a mammal, preferably 0.01 mg to 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The pharmaceutical compositions of the present invention comprise an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt, as an active ingredient and may also contain a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder, stabilizer and the like and optionally other ingredients used in pharmaceutical formulations. The compositions may also comprise one or more additional therapeutic agents. The compositions of this invention include compositions suitable for oral, rectal, topical, parenteral, ocular, pulmonary, or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of the pharmacy.

Dosage forms include tablets, troches, dragees, powders, syrups, patches, liposomes, injections, dispersions, suspensions, solutions, capsules, creams, ointments and aerosols. Compositions which provide from 0.1 to 10.0 mg of the active ingredient are preferred.

In general, an effective amount means that amount of a compound of this invention that will elicit the biological or medical response that is being sought. Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary and nasal administration, any be employed.

The Montelukast free acid used for the preparation of the novel anhydrous amorphous forms of Montelukast alkali salts is prepared as per processes known in the prior art.

The following examples illustrate the invention but do not construe to limit the same.

EXAMPLES

Reference Example

Preparation of Montelukast free acid

Montelukast dicyclohexylamine salt (250.0 g, 0.326 moles) is suspended in dichloromethane (2.5 lit.), followed by addition of water (1.25 lit.), acetic acid (28 ml, 0.489 moles). The mixture is stirred for 30 minutes at ambient temperature. The layers are separated and the aqueous layer extracted with dichloromethane (1 x 500ml and 1 x 125 ml). The combined organic layers are washed with water (4 x 1.25lit.) and the organic layer separated. The organic layer thus obtained is dried over anhydrous sodium sulfate. The reaction solution is decanted, solvent from the reaction solution distilled under vacuum at below 50°C to afford the Montelukast free acid as residual mass.

Example 1

Montelukast free acid (260 g.) is dissolved in toluene (500ml) and the solvent is completely distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (750ml) and 0.5M methanolic sodium hydroxide solution (665ml) added and the mixture stirred for 15-30 minutes. The solvent from the reaction mass is distilled off under reduced pressure at below 50°C, followed by addition of toluene (500 ml) and distilling off 10-30% (v/v) of the reaction volume under reduced pressure at below 50°C. The concentrated reaction solution is added to hexane (2.5lit.) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with hexane (500 ml), further the compound is filtered under vacuum. The wet compound was dried under vacuum at 70-80°C for 6-7 hours to yield amorphous form of Montelukast sodium. (Weight: 188 g., 94.90%, HPLC purity: 99.40%).

Example 2

Montelukast free acid (approx 26 g) is dissolved in toluene (50ml) and the solvent is completely distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (75ml) and 0.5M methanolic sodium hydroxide solution (69 ml) is added and the mixture stirred for 15-30 minutes. The solvent from the reaction mass was distilled off under reduced pressure at below 50^{O}C followed by addition of toluene (300 ml) and charcoal treatment. The solvent from the reaction solution is

distilled off completely under reduced pressure at below 50°C. The residual mass is dissolved in toluene (40 ml) and solution added to n-heptane (250 ml) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with n-heptane (50 ml), further the compound is filtered under vacuum and dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 18.0 g., 91.0%, HPLC purity: 99.40%)

Example 3

Montelukast free acid (14 g.) is dissolved in toluene (20 ml) and distilled off the solvent completely under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml) is added and reaction mass stirred for 15-30 minutes. The solvent from the reaction mass is distilled off under reduced pressure at below 50°C followed by addition of toluene (20 ml) and distilling the solvent to obtain 10-30% (v/v) of the reaction volume under reduced pressure at below 50°C. The concentrated reaction solution is added to cyclo hexane (100 ml.) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with cyclo hexane (20 ml), further the compound is filtered under vacuum. The wet compound is dried under vacuum at 70-85°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 6.8 g., 85.0%, HPLC purity: 99.10%).

Example 4

Montelukast free acid (0 g.) is dissolved in toluene (20ml) and the solvent is distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml) is added and reaction mass is stirred for 15-30 minutes. The solvent is distilled off completely under reduced pressure at below 50°C.

To the residue, dichloro methane (15 ml) is added. The resulting solution is added to n-heptane (200 ml) under nitrogen atmosphere for 15-30 minutes at ambient temperature. The reaction mass is stirred for 1-2 hours. The compound thus obtained is filtered under nitrogen atmosphere and washed with n-heptane (40 ml). The wet compound

was dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 6.3 g., 78.70%, HPLC purity: 99.10%).

Fig-1 is characteristic X-ray powder diffraction pattern of amorphous form of Montelukast Sodium Salt. Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

CLAIMS

1. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt).

2. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast Sodium).

3. The amorphous form according to claim 2, characterized by an X-ray powder diffraction pattern substantially in accordance with Fig-1.

4. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

isolating novel amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

5. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

6. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an sodium hydroxide or an sodium alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

7. A process for preparation of novel amorphous form of Montelukast Sodium, which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to the corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

8. The process according to claim 4 or 5 wherein the alkaline metal is sodium, calcium, magnesium or potassium.

9. The process according to claim 4, wherein the alkaline alkoxide is selected from sodium methoxide or sodium ethoxide.

10. The process according to claim 6, wherein the sodium alkoxide is sodium methoxide or sodium ethoxide.

11. The process according to claim 4, wherein the alkaline hydroxide is sodium hydroxide.

12. The process according to any one of claims 4 to 7, wherein the ratio of the free acid of Montelukast to C_1-C_2 halogenated solvent or C_7-C_8 aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.

13. The process according to claim 4 or 6, wherein the ratio of Montelukast to C_1-C_4 straight or branched chain alcohol is 1:2-3 w/v.

14. The process according to claim 4, wherein the molar ratio of Montelukast acid to alkaline metal hydroxide or alkaline metal alkoxide acid is 1:0.98 – 1.02.

15. The process according to claim 6, wherein the molar ratio of Montelukast acid to sodium hydroxide or sodium alkoxide is 1:0.98 – 1.02.

16. The process according to claim 5, wherein the molar ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v.

17. The process according to claim 7, wherein the molar ratio of Montelukast acid to alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1:2-4 w/v.

18. The process according to claim 5, wherein the molar ratio of Montelukast acid to alkali in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1: 0.98 – 1.02 w/v.

19. The process according to claim 7, wherein the molar ratio of Montelukast acid to sodium in alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1: 0.98 – 1.02 w/v.

20. The process according to any one of claims 4 to 7, wherein in step iii), the ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.

21. The process according to any one of claims 4 to 7, wherein in step iv) the ratio of C_1-C_2 halogenated solvent or C_7-C_8 aromatic solvent to the C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon is 1:5 to 1:13 v/v.

22. The process according to any one of claims 4 to 7, wherein the C_1-C_2 halogenated solvent is selected from chloroform, dichloromethane or dichloroethane.

23. The process according to claim 21, wherein the halogenated solvent is dichloromethane.

24. The process according to any one of claims 4 to 7, wherein the C_7-C_8 aromatic hydrocarbon solvent is selected from toluene, ethyl benzene or xylene.

25. The process according to claim 24, wherein the aromatic hydrocarbon solvent is toluene.

26. The process according to any one of claims 4 or 6, wherein the C_1-C_4 straight or branched chain alcohol is selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary butanol.

27. The process according to claim 26, wherein the C_1-C_4 straight or branched chain alcohol is methanol.

28. The process according to any one of claims 4 to 7, wherein the C_5-C_7 cyclic hydrocarbon solvent is selected from cyclopentane, cyclohexane or cycloheptane.

29. The process according to claim 27, wherein the cyclic hydrocarbon solvent is cyclohexane.

30. The process according to any one of claims 4 to 7, wherein the C_5-C_8 acyclic hydrocarbon solvent is selected from pentane, hexane, n-hexane, n-heptane or n-octane.

31. The process according to claim 29, wherein the acyclic hydrocarbon solvent is hexane or n-heptane.

32. A composition comprising an effective amount of a compound of any one of claims 1-3 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder or stabilizer.

33. The composition according to claim 31, in the form of a tablet, troche, dragee, powder, syrup, patch, liposome, injection, dispersion, suspension, solutions, capsule, cream, ointment or aerosol.

34. The use of a compound of any one of claims 1-3, for the manufacture of a medicament, for preventing the synthesis, the action, or the release of SRS-A or leukotrienes.

35. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating asthma.

36. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating inflammatory diseases of the eye.

37. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies or allergic reactions such as allergic rhinitis, contact dermatitis, or allergic conjunctivitis, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, or atopic eczema, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, or platelet aggregation 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, or endotoxemia, 12) allograft rejection, 13) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 4) cholecystitis, or 15) glomerular nephritis.

38. The use of a compound according to any one of claims 1 to 3, for prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor.

39. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea' ischemia, noxious agent-induced damage of necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatodxix agents; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; or glycerol-induced renal failure.

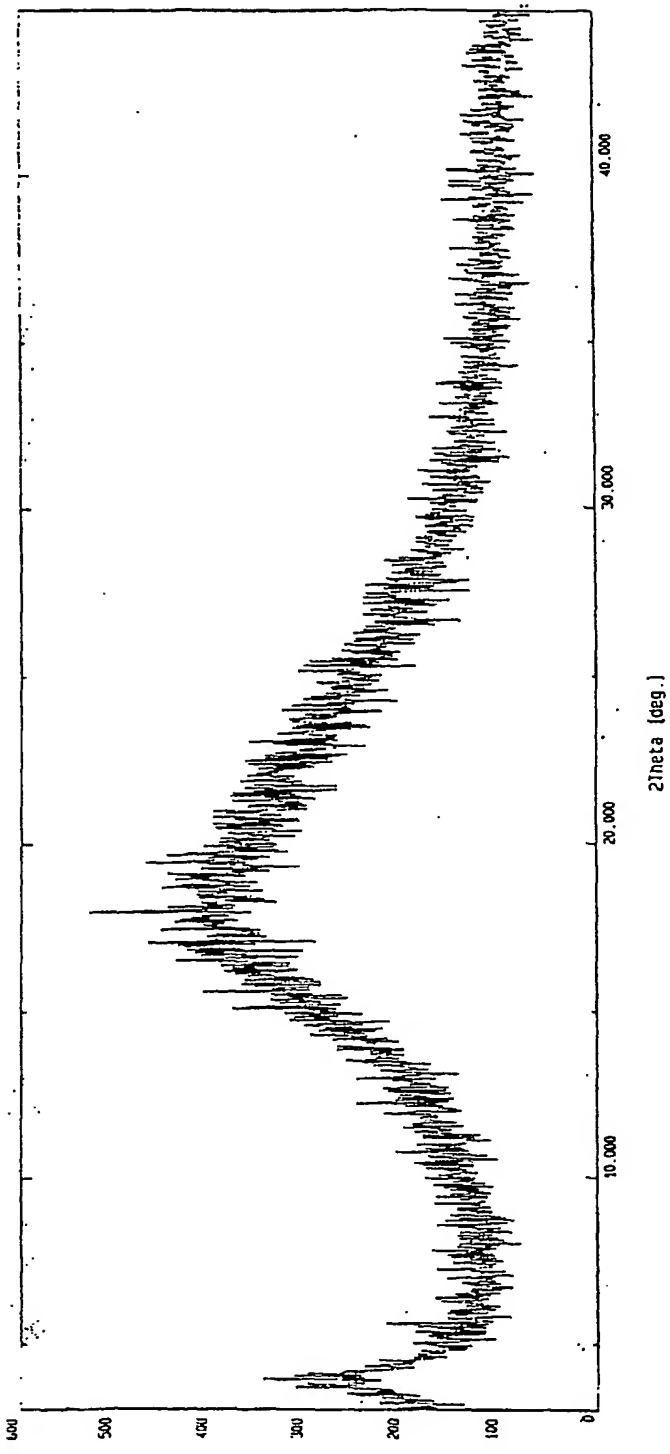


Fig. (1)

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/18 A61K31/47 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 480 717 A (MERCK FROSST CANADA INC) 15 April 1992 (1992-04-15) cited in the application page 68 -page 69; example 161	1,2, 32-39
A	---	3-31
A	WO 95 18107 A (MERCK & CO INC ;BHUPATHY MAHADEVAN (US); MCNAMARA JAMES M (US); SI) 6 July 1995 (1995-07-06) examples 8,14	1-39

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2003	09/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kollmannsberger, M

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0480717 A	15-04-1992	AT 165088 T	15-05-1998
		AU 639610 B2	29-07-1993
		AU 8579491 A	16-04-1992
		BR 1100383 A3	25-07-2000
		CA 2053209 A1	13-04-1992
		CN 1061407 A ,B	27-05-1992
		CS 9103095 A3	15-04-1992
		DE 69129257 D1	20-05-1998
		DE 69129257 T2	05-11-1998
		DK 480717 T3	08-02-1999
		EP 0480717 A1	15-04-1992
		ES 2114882 T3	16-06-1998
		FI 914796 A	13-04-1992
		FI 20000250 A	07-02-2000
		HK 1027473 A1	12-01-2001
		HR 930751 A1	30-06-1995
		HU 61981 A2	29-03-1993
		HU 9500178 A3	28-08-1995
		IE 913609 A1	22-04-1992
		IL 99726 A	22-02-1998
		IL 117147 A	31-10-2000
		JP 2501385 B2	29-05-1996
		JP 5105665 A	27-04-1993
		KR 227716 B1	01-11-1999
		LU 90284 A9	03-11-1998
		LV 12187 A	20-12-1998
		LV 12187 B	20-02-1999
		MX 9101551 A1	05-06-1992
		NZ 240194 A	28-03-1995
		PT 99213 A ,B	30-09-1992
		SI 9111647 A ,B	31-12-1997
		SK 279944 B6	11-06-1999
		US 5565473 A	15-10-1996
		US 5856322 A	05-01-1999
		ZA 9108119 A	26-08-1992
		NO 923099 A ,B,	09-02-1993
		NO 960426 A ,B,	09-02-1993
WO 9518107 A	06-07-1995	AT 169906 T	15-09-1998
		AU 686303 B2	05-02-1998
		AU 1444895 A	17-07-1995
		BG 62850 B1	29-09-2000
		BG 100638 A	31-03-1997
		BR 9408452 A	05-08-1997
		CA 2179407 A1	06-07-1995
		CN 1139429 A ,B	01-01-1997
		CN 1219535 A	16-06-1999
		CZ 9601878 A3	11-12-1996
		DE 69412644 D1	24-09-1998
		DE 69412644 T2	11-02-1999
		DK 737186 T3	08-02-1999
		EP 0737186 A1	16-10-1996
		ES 2122534 T3	16-12-1998
		FI 962641 A	26-06-1996
		HK 1009269 A1	24-08-2001
		HR 941022 A1	30-06-1997
		HU 76279 A2	28-07-1997
		JP 9507235 T	22-07-1997

INTERNATIONAL SEARCH REPORT
nformation on patent family members

ational Application No
PCT/US 03/03700

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9518107 A		LV	12313 B	20-11-1999
		NZ	278263 A	27-04-1998
		PL	315155 A1	14-10-1996
		RU	2140909 C1	10-11-1999
		TW	416948 B	01-01-2001
		TW	448160 B	01-08-2001
		WO	9518107 A1	06-07-1995
		US	6320052 B1	20-11-2001
		US	5614632 A	25-03-1997
		LV	12313 A	20-07-1999

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(74) Agents: **CORD, Janet, I.** et al.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
— *with international search report*

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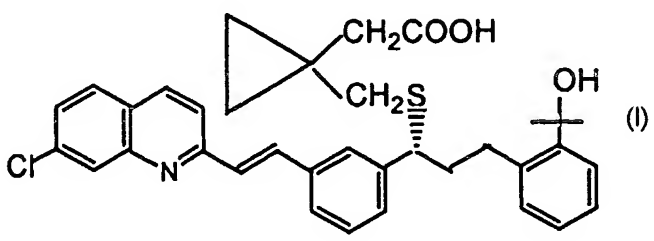
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT



(I)

by the formula (I).

(57) Abstract: The present invention relates to novel anhydrous amorphous forms of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same. Montelukast is a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent. Montelukast is represented

WO 03/066598 A1

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
94/MAS/2002		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 03/03700	07/02/2003	07/02/2002
Applicant		
DR. REDDY'S LABORATORIES LTD.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

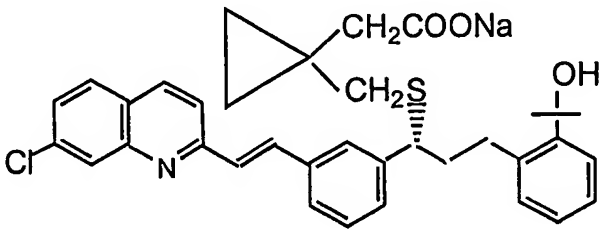
   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

NOVEL ANHYDROUS AMORPHOUS FORMS OF MONTELUKAST SODIUM SALT

The present invention relates to novel anhydrous amorphous forms of [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) to processes for their preparation, to compositions containing them and to methods of treatment using the same.

Montelukast Sodium, chemically known as [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid (Montelukast) sodium salt is represented by the formula:



Montelukast sodium, a leukotriene antagonist, is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and is hence useful in the treatment of angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection.

EP 480717 discloses certain substituted quinoline compounds including [R-(E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium), and methods for their preparation.

The reported synthesis of Montelukast Sodium proceeds through corresponding methyl ester and involves coupling methyl 1-(mercaptomethyl) cyclopropane-acetate with a mesylate generated *in situ*. The methyl ester of Montelukast free acid is hydrolyzed to the free acid and the latter converted directly to the corresponding sodium salt. This process is not particularly suitable for large-scale production because it requires tedious chromatographic purification of the methyl ester intermediate and/or the final product, and the product yields are low.

WO Patent Application 95/18107 discloses an improved process for the preparation of crystalline Montelukast sodium salt, which comprises the generation of dilithium dianion of 1-(mercaptomethyl) cyclopropaneacetic acid followed by condensation with 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl) ethenyl) phenyl)-3-methanesulfonyloxypropyl) phenyl)-2-propanol to afford the Montelukast acid which is then converted, via dicyclohexyl amine salt, to its corresponding sodium salt. The obtained sodium salt is further crystallized from a mixture of toluene: acetonitrile to obtain crystalline Montelukast sodium.

The PCT application further designates the products obtained as per EP 480717 as amorphous sodium salts, which are hydrated and often not ideal for pharmaceutical formulation.

It has been disclosed earlier that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms [Konne T., Chem pharm Bull., 38, 2003(1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. An amorphous form of Cefuroxime axetil is a good example for exhibiting higher bioavailability than the crystalline form.

Since Montelukast sodium is useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agent and amorphous forms of a number of drugs have been disclosed to exhibit different dissolution characteristics and in some cases different bioavailability patterns when compared to crystalline forms, the present invention, hence, aims to provide novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts and to processes for the preparation thereof.

The present invention also provides pharmaceutical compositions and pharmaceutical methods of treatment using novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

Another embodiment of the present invention is to provide methods for the preparation of the anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts (Montelukast alkali salts) which comprises dissolution of

Montelukast free acid in aromatic hydrocarbon solvent or halogenated solvent and converting the free acid to its alkali salt, accompanied by addition of a cyclic or acyclic hydrocarbon solvent or mixtures thereof, followed by isolation of the desired compound.

Still another embodiment of the present invention is to provide pharmaceutical formulations containing an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt.

An additional embodiment of the present invention is to provide pharmaceutical methods of treatment using anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts.

Brief Description Of The Accompanying Drawing

Fig. 1 is X-ray powder diffractogram of novel anhydrous amorphous form of Montelukast Sodium.

The present invention provides novel anhydrous amorphous forms of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salts, preferably, anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt.

The present invention also provides a process for preparation of anhydrous amorphous forms of Montelukast alkali metal salts. The anhydrous amorphous forms of Montelukast alkali metal salts are prepared by dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon. The solution of free acid of Montelukast is converted into alkali salt by use of alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C_1-C_4 straight or branched chain alcohol or by use of alcoholic alkaline metal hydroxide or an alcoholic metal alkoxide.

One process for preparing amorphous forms of Montelukast alkali metal salts comprises:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in the presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent; and

iv) isolating amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of amorphous forms of Montelukast alkali metal salts, which comprises:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent; and

iv) isolating amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

The alkaline metal may be selected from calcium, sodium, potassium, or magnesium. Preferably, the alkaline metal is sodium.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

i) dissolving the free acid of Montelukast sodium in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding sodium salt using sodium hydroxide or sodium alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

According, to another embodiment, the present invention provides a process for preparation of novel anhydrous amorphous form of Montelukast Sodium, which comprises:

i) dissolving the free acid of Montelukast sodium in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating anhydrous amorphous form of Montelukast alkali salt sodium by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

In a preferred embodiment of the invention, the ratio of Montelukast free acid to C_1-C_2 halogenated solvent or C_7-C_8 aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.

In a preferred embodiment of the invention, the ratio of Montelukast acid to C_1-C_4 straight or branched chain alcohol is 1:2-3 w/v.

In a preferred embodiment of the invention, the molar ratio of Montelukast acid to alkali metal hydroxide or alkaline metal alkoxide is 1:0.98 – 1.02, preferably, 1:1. In a preferred embodiment of the invention, the ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v wherein the ratio of Montelukast acid to alkaline metal in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:0.98 – 1.02 w/v. In step iii), the ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.

In precipitation of Montelukast alkali salt in step iv) the ratio of C_1-C_2 halogenated solvent or C_7-C_8 aromatic solvent to the C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon is 1:5 to 1:13 v/v. The preferred ratio is 1:6.5 v/v. This ratio is based on the amount of the C_1-C_2 halogenated solvent or C_7-C_8 solvent added in step iii).

The C_1-C_2 halogenated solvent may be selected from chloroform, dichloromethane or dichloroethane, preferably dichloromethane. The C_7-C_8 aromatic hydrocarbon solvent may be selected from toluene, ethyl benzene or xylene, preferably toluene.

The alkali used in step ii) may be selected from sodium hydroxide, sodium methoxide, sodium ethoxide, methanolic sodium hydroxide, ethanolic sodium hydroxide, methanolic sodium methoxide, ethanolic sodium methoxide, methanolic sodium ethoxide, ethanolic sodium ethoxide, calcium hydroxide, calcium methoxide, calcium ethoxide, methanolic calcium hydroxide, ethanolic calcium hydroxide, methanolic calcium methoxide, ethanolic calcium methoxide, methanolic calcium ethoxide, ethanolic calcium ethoxide, potassium hydroxide, potassium methoxide, potassium ethoxide, methanolic potassium hydroxide, ethanolic potassium hydroxide, methanolic potassium methoxide, ethanolic potassium methoxide, methanolic potassium ethoxide, ethanolic potassium ethoxide, magnesium hydroxide, magnesium methoxide, magnesium ethoxide, methanolic magnesium hydroxide, ethanolic magnesium hydroxide, methanolic magnesium methoxide, ethanolic magnesium methoxide, methanolic magnesium ethoxide, ethanolic magnesium ethoxide, preferably the alkali is sodium hydroxide.

The C_1-C_4 straight or branched chain alcohol may be selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary.butanol, preferably methanol. The C_5-C_7 acyclic solvent may be selected from pentane, hexane, n-hexane, n-heptane or n-octane, preferably hexane or n-heptane. The C_5-C_8 cyclic hydrocarbon solvent may be selected from cyclopentane, cyclohexane or cycloheptane, preferably cyclohexane.

Novel anhydrous amorphous forms of Montelukast alkali salts may be characterized by the X-Ray powder diffraction pattern. The present invention provides anhydrous amorphous form of Montelukast Sodium that is characterized by its X Ray powder diffraction, substantially in accordance with Figure 1. The X-Ray diffraction pattern of anhydrous amorphous form of Montelukast Sodium was measured on a Rigaku Dmax 2000 with Cu K alpha-1 ISOKV/34mA, Degrees scanned: 3-45 degrees. Scan speed 3 degree/min.

The compounds of this invention can be used to prevent the synthesis, the action or the release of SRS-A or leukotrienes.

The ability of the compounds of the present invention to antagonize the actions of the leukotrienes makes them useful for preventing or reversing the symptoms induced by the leukotrienes in a mammal including a human subject. This antagonism of the actions of leukotrienes indicates that the compounds of this invention and pharmaceutical compositions thereof are useful to treat, prevent, or ameliorate in mammals and especially in humans: 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies and allergic reactions such as allergic rhinitis, contact, allergic conjunctivitis, and the like, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, atopic eczema, and the like, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, platelet aggregation and the like, 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions including inflammatory diseases such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, endotoxemia and the like, 12) allograft rejection, 13) prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor, 14) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 15) cholecystitis and 16) glomerular nephritis.

The compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea' ischemia, noxious agent-induced damage of necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatodxix agents such as CCl_4 and D-galactosamine; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure. The compounds also exhibit cytoprotective action. (See EP 0480717).

The magnitude of prophylactic or therapeutic dose of a compound of this invention will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of this invention and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range for anti-asthmatic, anti-allergic or anti-inflammatory use and generally, uses other

than cytoprotection, lie within the range of from 0.001 mg to 100 mg per kg body weight of a mammal, preferably 0.01 mg to 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The pharmaceutical compositions of the present invention comprise an anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt, as an active ingredient and may also contain a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder, stabilizer and the like and optionally other ingredients used in pharmaceutical formulations. The compositions may also comprise one or more additional therapeutic agents. The compositions of this invention include compositions suitable for oral, rectal, topical, parenteral, ocular, pulmonary, or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of the pharmacy.

Dosage forms include tablets, troches, dragees, powders, syrups, patches, liposomes, injections, dispersions, suspensions, solutions, capsules, creams, ointments and aerosols. Compositions which provide from 0.1 to 10.0 mg of the active ingredient are preferred.

In general, an effective amount means that amount of a compound of this invention that will elicit the biological or medical response that is being sought. Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary and nasal administration, any be employed.

The Montelukast free acid used for the preparation of the novel anhydrous amorphous forms of Montelukast alkali salts is prepared as per processes known in the prior art.

The following examples illustrate the invention but do not construe to limit the same.

EXAMPLES

Reference Example

Preparation of Montelukast free acid

Montelukast dicyclohexylamine salt (250.0 g, 0.326 moles) is suspended in dichloromethane (2.5 lit.), followed by addition of water (1.25 lit.), acetic acid (28 ml, 0.489 moles). The mixture is stirred for 30 minutes at ambient temperature. The layers are separated and the aqueous layer extracted with dichloromethane (1 x 500ml and 1 x 125 ml). The combined organic layers are washed with water (4 x 1.25lit.) and the organic layer separated. The organic layer thus obtained is dried over anhydrous sodium sulfate. The reaction solution is decanted, solvent from the reaction solution distilled under vacuum at below 50°C to afford the Montelukast free acid as residual mass.

Example 1

Montelukast free acid (260 g.) is dissolved in toluene (500ml) and the solvent is completely distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (750ml) and 0.5M methanolic sodium hydroxide solution (665ml) added and the mixture stirred for 15-30 minutes. The solvent from the reaction mass is distilled off under reduced pressure at below 50°C, followed by addition of toluene (500 ml) and distilling off 10-30% (v/v) of the reaction volume under reduced pressure at below 50°C. The concentrated reaction solution is added to hexane (2.5lit.) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with hexane (500 ml), further the compound is filtered under vacuum. The wet compound was dried under vacuum at 70-80°C for 6-7 hours to yield amorphous form of Montelukast sodium. (Weight: 188 g., 94.90%, HPLC purity: 99.40%).

Example 2

Montelukast free acid (approx 26 g) is dissolved in toluene (50ml) and the solvent is completely distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (75ml) and 0.5M methanolic sodium hydroxide solution (69 ml) is added and the mixture stirred for 15-30 minutes. The solvent from the reaction mass was distilled off under reduced pressure at below 50^{O}C followed by addition of toluene (300 ml) and charcoal treatment. The solvent from the reaction solution is

distilled off completely under reduced pressure at below 50°C. The residual mass is dissolved in toluene (40 ml) and solution added to n-heptane (250 ml) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with n-heptane (50 ml), further the compound is filtered under vacuum and dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 18.0 g., 91.0%, HPLC purity: 99.40%)

Example 3

Montelukast free acid (14 g.) is dissolved in toluene (20 ml) and distilled off the solvent completely under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml) is added and reaction mass stirred for 15-30 minutes. The solvent from the reaction mass is distilled off under reduced pressure at below 50°C followed by addition of toluene (20 ml) and distilling the solvent to obtain 10-30% (v/v) of the reaction volume under reduced pressure at below 50°C. The concentrated reaction solution is added to cyclo hexane (100 ml.) under Nitrogen atmosphere for 15-30 minutes at ambient temperature and stirred for 1-2 hours. The desired isolated compound is filtered under Nitrogen atmosphere and washed with cyclo hexane (20 ml), further the compound is filtered under vacuum. The wet compound is dried under vacuum at 70-85°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 6.8 g., 85.0%, HPLC purity: 99.10%).

Example 4

Montelukast free acid (0 g.) is dissolved in toluene (20ml) and the solvent is distilled off under vacuum at below 50°C to afford the residue. The residue thus obtained is further dissolved in toluene (30ml) and 0.5M methanolic sodium hydroxide solution (27 ml) is added and reaction mass is stirred for 15-30 minutes. The solvent is distilled off completely under reduced pressure at below 50°C.

To the residue, dichloro methane (15 ml) is added. The resulting solution is added to n-heptane (200 ml) under nitrogen atmosphere for 15-30 minutes at ambient temperature. The reaction mass is stirred for 1-2 hours. The compound thus obtained is filtered under nitrogen atmosphere and washed with n-heptane (40 ml). The wet compound

was dried under vacuum at 70-80°C for 2-3 days to yield amorphous form of Montelukast sodium. (Weight: 6.3 g., 78.70%, HPLC purity: 99.10%).

Fig-1 is characteristic X-ray powder diffraction pattern of amorphous form of Montelukast Sodium Salt. Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

CLAIMS

1. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt).

2. Novel anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast Sodium).

3. The amorphous form according to claim 2, characterized by an X-ray powder diffraction pattern substantially in accordance with Fig-1.

4. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alkaline metal hydroxide or an alkaline metal alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

isolating novel amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

5. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid alkali salt (Montelukast alkali salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

6. A process for the preparation of anhydrous amorphous form of [R- (E)-1-[[[1-[3-[2-[7-chloro-2-quinolinyl] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid sodium salt (Montelukast sodium salt), which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to corresponding alkali salt using an sodium hydroxide or an sodium alkoxide in presence of C_1-C_4 straight or branched chain alcohol, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

7. A process for preparation of novel amorphous form of Montelukast Sodium, which comprises the steps of:

i) dissolving the free acid of Montelukast in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent;

ii) converting the dissolved acid of step i) to the corresponding sodium salt using alcoholic sodium hydroxide or alcoholic sodium alkoxide, followed by;

iii) optionally dissolving the reaction mass of step ii) in C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent, and

iv) isolating novel amorphous form of Montelukast sodium by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon.

8. The process according to claim 4 or 5 wherein the alkaline metal is sodium, calcium, magnesium or potassium.

9. The process according to claim 4, wherein the alkaline alkoxide is selected from sodium methoxide or sodium ethoxide.

10. The process according to claim 6, wherein the sodium alkoxide is sodium methoxide or sodium ethoxide.

11. The process according to claim 4, wherein the alkaline hydroxide is sodium hydroxide.

12. The process according to any one of claims 4 to 7, wherein the ratio of the free acid of Montelukast to C_1-C_2 halogenated solvent or C_7-C_8 aromatic hydrocarbon solvent in step i) is 1:1.5 to 1:6 w/v.

13. The process according to claim 4 or 6, wherein the ratio of Montelukast to C_1-C_4 straight or branched chain alcohol is 1:2-3 w/v.

14. The process according to claim 4, wherein the molar ratio of Montelukast acid to alkaline metal hydroxide or alkaline metal alkoxide acid is 1:0.98 – 1.02.

15. The process according to claim 6, wherein the molar ratio of Montelukast acid to sodium hydroxide or sodium alkoxide is 1:0.98 – 1.02.

16. The process according to claim 5, wherein the molar ratio of Montelukast acid to alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1:2-4 w/v.

17. The process according to claim 7, wherein the molar ratio of Montelukast acid to alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1:2-4 w/v.

18. The process according to claim 5, wherein the molar ratio of Montelukast acid to alkali in alcoholic alkaline metal hydroxide or alcoholic alkaline metal alkoxide is 1: 0.98 – 1.02 w/v.

19. The process according to claim 7, wherein the molar ratio of Montelukast acid to sodium in alcoholic sodium hydroxide or alcoholic sodium alkoxide is 1: 0.98 – 1.02 w/v.

20. The process according to any one of claims 4 to 7, wherein in step iii), the ratio of the reaction mass to the solvent is 1:1.2 to 1:4 w/v.

21. The process according to any one of claims 4 to 7, wherein in step iv) the ratio of C_1-C_2 halogenated solvent or C_7-C_8 aromatic solvent to the C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon is 1:5 to 1:13 v/v.

22. The process according to any one of claims 4 to 7, wherein the C_1-C_2 halogenated solvent is selected from chloroform, dichloromethane or dichloroethane.

23. The process according to claim 21, wherein the halogenated solvent is dichloromethane.

24. The process according to any one of claims 4 to 7, wherein the C_7-C_8 aromatic hydrocarbon solvent is selected from toluene, ethyl benzene or xylene.

25. The process according to claim 24, wherein the aromatic hydrocarbon solvent is toluene.

26. The process according to any one of claims 4 or 6, wherein the C_1-C_4 straight or branched chain alcohol is selected from methanol, ethanol, propanol, butanol, 2-propanol or tertiary butanol.

27. The process according to claim 26, wherein the C_1-C_4 straight or branched chain alcohol is methanol.

28. The process according to any one of claims 4 to 7, wherein the C_5-C_7 cyclic hydrocarbon solvent is selected from cyclopentane, cyclohexane or cycloheptane.

29. The process according to claim 27, wherein the cyclic hydrocarbon solvent is cyclohexane.

30. The process according to any one of claims 4 to 7, wherein the C_5-C_8 acyclic hydrocarbon solvent is selected from pentane, hexane, n-hexane, n-heptane or n-octane.

31. The process according to claim 29, wherein the acyclic hydrocarbon solvent is hexane or n-heptane.

32. A composition comprising an effective amount of a compound of any one of claims 1-3 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, solvent, binder or stabilizer.

33. The composition according to claim 31, in the form of a tablet, troche, dragee, powder, syrup, patch, liposome, injection, dispersion, suspension, solutions, capsule, cream, ointment or aerosol.

34. The use of a compound of any one of claims 1-3, for the manufacture of a medicament, for preventing the synthesis, the action, or the release of SRS-A or leukotrienes.

35. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating asthma.

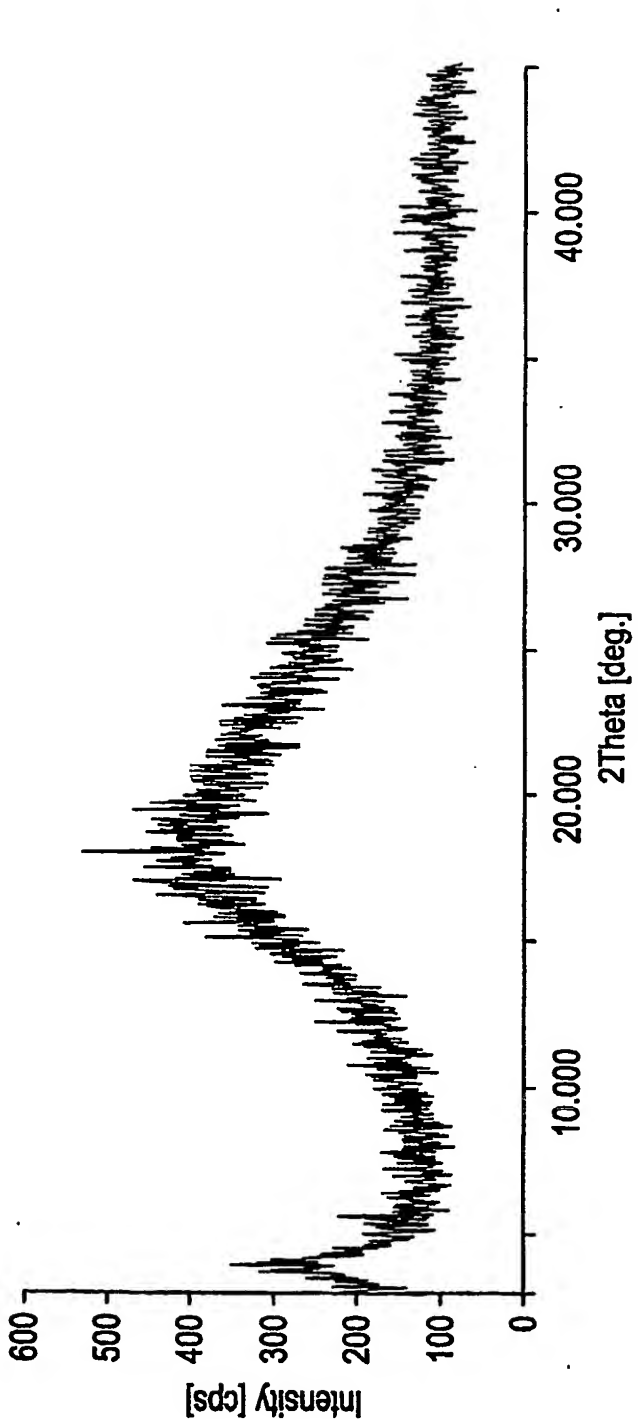
36. The use of a compound of any one of claims 1-3, for the manufacture of a medicament for treating inflammatory diseases of the eye.

37. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies or allergic reactions such as allergic rhinitis, contact dermatitis, or allergic conjunctivitis, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as psoriasis, or atopic eczema, 6) conditions related to cardiovascular disorders such as angina, myocardial ischemia, hypertension, or platelet aggregation 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, 8) migraine or cluster headache, 9) ocular conditions such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, or endotoxemia, 12) allograft rejection, 13) chronic lung diseases such as cystic fibrosis, bronchitis and other small and large-airway diseases, 4) cholecystitis, or 15) glomerular nephritis.

38. The use of a compound according to any one of claims 1 to 3, for prevention of side effects associated with therapeutic administration of cytokines such as interleukin II and tumor necrosis factor.

39. The use of a compound of any one of claims 1 to 3, for preparing a medicament for treating, preventing or ameliorating erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion, dysmenorrhea' ischemia, noxious agent-induced damage of necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatodxix agents; ischaemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; or glycerol-induced renal failure.

FIG. 1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INTERNATIONAL SEARCH REPORT

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PCT/US 03/03700

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/18 A61K31/47 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 480 717 A (MERCK FROSST CANADA INC) 15 April 1992 (1992-04-15) cited in the application page 68 -page 69; example 161	1,2, 32-39
A	---	3-31
A	WO 95 18107 A (MERCK & CO INC ;BHUPATHY MAHADEVAN (US); MCNAMARA JAMES M (US); SI) 6 July 1995 (1995-07-06) examples 8,14	1-39

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2003	09/05/2003

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No
PCT/US 03/03700

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0480717 A	15-04-1992	AT 165088 T	15-05-1998
		AU 639610 B2	29-07-1993
		AU 8579491 A	16-04-1992
		BR 1100383 A3	25-07-2000
		CA 2053209 A1	13-04-1992
		CN 1061407 A ,B	27-05-1992
		CS 9103095 A3	15-04-1992
		DE 69129257 D1	20-05-1998
		DE 69129257 T2	05-11-1998
		DK 480717 T3	08-02-1999
		EP 0480717 A1	15-04-1992
		ES 2114882 T3	16-06-1998
		FI 914796 A	13-04-1992
		FI 20000250 A	07-02-2000
		HK 1027473 A1	12-01-2001
		HR 930751 A1	30-06-1995
		HU 61981 A2	29-03-1993
		HU 9500178 A3	28-08-1995
		IE 913609 A1	22-04-1992
		IL 99726 A	22-02-1998
		IL 117147 A	31-10-2000
		JP 2501385 B2	29-05-1996
		JP 5105665 A	27-04-1993
		KR 227716 B1	01-11-1999
		LU 90284 A9	03-11-1998
		LV 12187 A	20-12-1998
		LV 12187 B	20-02-1999
		MX 9101551 A1	05-06-1992
		NZ 240194 A	28-03-1995
		PT 99213 A ,B	30-09-1992
		SI 9111647 A ,B	31-12-1997
		SK 279944 B6	11-06-1999
		US 5565473 A	15-10-1996
		US 5856322 A	05-01-1999
		ZA 9108119 A	26-08-1992
		NO 923099 A ,B,	09-02-1993
		NO 960426 A ,B,	09-02-1993
WO 9518107 A	06-07-1995	AT 169906 T	15-09-1998
		AU 686303 B2	05-02-1998
		AU 1444895 A	17-07-1995
		BG 62850 B1	29-09-2000
		BG 100638 A	31-03-1997
		BR 9408452 A	05-08-1997
		CA 2179407 A1	06-07-1995
		CN 1139429 A ,B	01-01-1997
		CN 1219535 A	16-06-1999
		CZ 9601878 A3	11-12-1996
		DE 69412644 D1	24-09-1998
		DE 69412644 T2	11-02-1999
		DK 737186 T3	08-02-1999
		EP 0737186 A1	16-10-1996
		ES 2122534 T3	16-12-1998
		FI 962641 A	26-06-1996
		HK 1009269 A1	24-08-2001
		HR 941022 A1	30-06-1997
		HU 76279 A2	28-07-1997
		JP 9507235 T	22-07-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

[redacted]national Application No
PCT/US 03/03700

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9518107 A		LV	12313 B	20-11-1999
		NZ	278263 A	27-04-1998
		PL	315155 A1	14-10-1996
		RU	2140909 C1	10-11-1999
		TW	416948 B	01-01-2001
		TW	448160 B	01-08-2001
		WO	9518107 A1	06-07-1995
		US	6320052 B1	20-11-2001
		US	5614632 A	25-03-1997
		LV	12313 A	20-07-1999